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EFFECTS OF ANTI-CONVULSANT MEDICATION ON SLEEP PATTERNS.(U)
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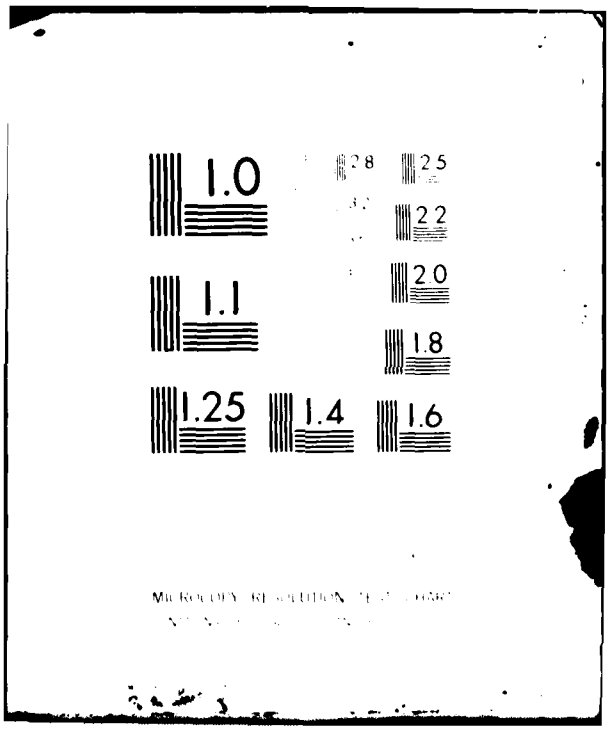
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EFFECTS OF ANTI-CONVULSANT MEDICATION ON SLEEP PATTERNS

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REPORT NO. 81-26

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NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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EFFECTS OF ANTI-CONVULSANT MEDICATION ON SLEEP PATTERNS

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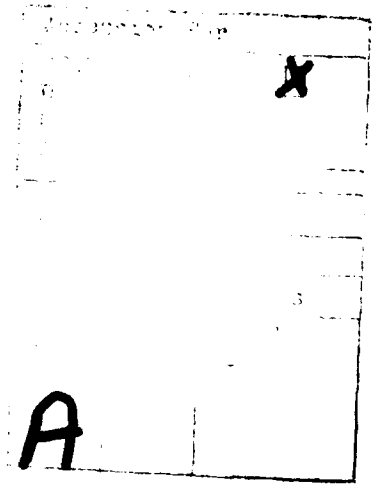


Report No. 81-26, supported by Naval Medical Research and Development Command, Bethesda, Maryland, Department of the Navy, under research Work Unit MR041.01.003-0157. The views presented in this paper are those of the author. No endorsement by the Department of the Navy has been given or should be inferred.

Presented at the International Symposium on Sleep and Epilepsy, Montpellier, France, 6-8 July 1981.

SUMMARY

A review of the published literature on effects of anti-convulsant medication on sleep patterns revealed few studies. The paucity of studies is probably due to the fact that all-night EEG-recorded sleep studies are not part of the usual diagnostic procedures for seizure patients. Seizure patients are seldom referred to the sleep laboratories and clinics, where the all-night sleep recording is routine. Also, few patients are treated by a single convulsant.

Most studies have used barbiturates, and the effects of this class of drug on sleep stages appear to be the same whether the barbiturate is prescribed as an anti-convulsant or sedative-hypnotic. The same sleep stage changes are also found for the benzodiazepines used as a sedative-hypnotic and as an anti-convulsant. Acute studies indicate that anti-convulsants decrease REM sleep, while chronic ingestion decreases SWS, but total amount of NREM sleep is less affected. Sleep spindles usually are increased. An epileptic patient's sleep pattern is most likely to be more normal or stabilized after effective treatment. This normalization appears to be due to the control of nocturnal seizures, which previously disrupted sleep, rather than due to any effect of the anti-convulsant per se on sleep patterns.

At the time I was invited to present a paper on effects of anti-convulsants on sleep patterns, I was preparing a review paper on sedative-hypnotics and human performance. As I had over 400 reprints on my desk dealing with drugs and sleep, I thought preparing a paper detailing the effects of anti-convulsant medication on sleep patterns would be no problem at all. Preparing the paper, however, has not been as easy as I had hoped. The first thing I found was that there have been few studies specifically dealing with sleep and anti-convulsant medication. I then asked our librarian to do a computer search requesting a listing of studies concerned with anti-convulsants, all types, and sleep. The search on medline turned up 15 citations, and the search using the epilepsy file provided an additional 33 articles. Only 10 of these articles reported nighttime sleep, and only 4 referred to or reported sleep stage data.[1-4]

There are several reasons for this lack of sleep data, and many of these reasons are obvious. In most instances, the epileptic patient, if he/she comes to the sleep laboratory, does so after being on one or more medications for days, weeks, or even years. Very seldom is only one medication used. In patients who have not been treated, there is the problem of determining after medication is started, whether the sleep changes seen, if any, are due to the effects of medication per se, or due to the change in seizure activity which directly influenced sleep, or due to the change in life style, mood, or other factors related to the efficacy of the anti-convulsant. Also, many convulsant patients have medical problems that are causally related to the seizure problem, and these medical problems may affect sleep. But perhaps of more importance than the medical or treatment factors is that most sleep researchers are not involved in recording epileptic patients, and the neurologists that do most of the EEG recordings on epileptics do not record all-night sleep. At this point, it is appropriate that I give my view of REM, NREM sleep, since I have raised questions when others of this symposium have presented their views on these sleep phenomena.

First, I believe that awake and not sleep is the preferred state of humans. We sleep only as long as needed to function effectively during the day. The necessary amount of sleep varies from person to person. We can, although with increasing difficulty, remain awake for many hours, and even days, but we cannot force ourselves to remain asleep. A young man in our laboratory went 11 days without sleep, but, even after this prolonged period of wakefulness, he was able to remain asleep only 14 hours and 40 minutes.[5] Further, during sleep itself, there are both brief phasic events, the K-complex for example, and longer periods, such as REM sleep, that maintain the plasticity of the nervous system and, thus, insure easy transition back into the awake state. It is my contention that if we were to remain in NREM sleep, and especially slow wave sleep (SWS) with its reduced level of physiological activity, for several hours, our ability to function upon awakening would be seriously impaired. To prevent this diminished capacity upon awakening, during sleep there is the transition between the relatively quiet NREM period and the active awake-like period of REM sleep. It is this cycling between REM and NREM that helps to maintain plasticity. Further, our ability to function more efficiently when we arouse from an awake-like state such as REM may explain why more REM periods occur in the latter period of sleep and most SWS is found in the first third of the night. I do not believe REM sleep is a period of sub-convulsive seizure activity, as has been suggested. I have presented a more expanded discussion of the above point of view in a paper which discusses the relationship of stages of sleep to awake behavior.[6]

In addition, I do not believe that the rapid eye movements (REMs) are related to the amount of light exposure or to dream content. When we are awake, we engage in constant REMs, an activity

necessary to maintain visual acuity. These REMs are under conscious control and do not have a well-defined and stable activity pattern but are related to conscious visual scanning. I suspect that the REMs during sleep reflect this same awake visual oculomotor activity, but during REM sleep, the REMs are "free running," if you will. Their pattern of activity reflects endogenous physiological firing patterns. This endogenous pattern is reflected in the unique pattern of REMs from subject to subject and their stability from one night to another.[7]

Acute Effects. Returning to the major topic of this paper, I will first present some acute effects of anti-convulsants on sleep, as these data are more numerous. Most of these acute studies have been done with the barbiturate, phenobarbital, which is a common anti-convulsant, but the barbiturates used as sedative-hypnotics produce the same electroencephalographic (EEG) changes during sleep. The other class of medication that has been widely used in sleep studies is the benzodiazepines. This class of drug has anti-convulsant properties, but only clonazepam is specifically marketed as an anti-convulsant. I could find no all-night sleep study using clonazepam that reported sleep stage data, but I assume its effect on the sleep EEG is similar to that of other benzodiazepines. In a conversation with Dr. Tom Roth at the recent sleep meetings, he confirmed that clonazepam does produce the expected benzodiazepine EEG changes. Except for diphenylhydantoin (DPH) with one clinical study[1] and one study on normal subjects,[8] I could find no reported all-night sleep data for the other usually prescribed anti-convulsants. One common side effect of anti-convulsants, of course, is drowsiness, but this unwanted sleep has not been a subject of scrutiny by the sleep researchers.

Sleep Patterns. If one examines the effects of acute administration of anti-convulsants in normal subjects, there is seldom a report of medication-induced changes in sleep patterns or structure. By pattern and structure, I am referring to the presence of all the sleep stages, the expected transition from one stage to another, and whether the duration of the REM-NREM cycle falls within the expected range. In seizure patients, if a change in sleep pattern is noted, it is most often reported as "a more normal pattern" or "the sleep pattern was stabilized." This stabilization is most likely to be reported in patients with nocturnal seizures, especially myoclonic seizures. Such was the case in the pre- and post-medication sleep profiles of an 8-year-old boy reported by Fukuyama *et al.*[1] The changes in sleep structure are illustrated in Fig. 1.

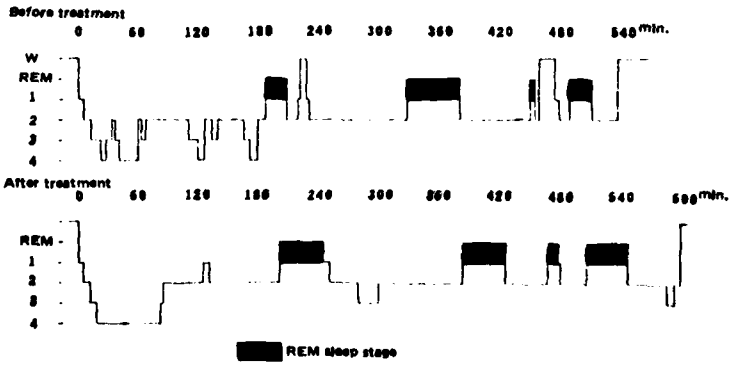


Fig. 1. Diagrams of overnight sleep course before and after treatment (from Fukuyama *et al.*[1]).

Over a year of treatment with DPH 100 mg, total sleep time increased from 496 to 594 minutes. Stage 2 decreased from 64% to 58%, while stage 4 increased from 6.9 to 10.8%. REM increased from 19 to 22%. Perhaps the most important indicator of the increased stability of sleep during treatment was the decrease in number of stage changes from 35 to 23. Thus, in the epileptic, if there is a change in sleep pattern, it is often that of normalizing or stabilizing the sleep. This stabilization appears to be due to the medication's action on the seizures per se, allowing more normal sleep to occur rather than due to the anti-convulsant's effect on sleep. The increase in SWS is usually associated with a cessation of the myoclonic seizures, the absence of the myoclonic activity permitting entry into SWS.

Dr. Alain Muzet (CNRS, Strasbourg, France), while in our laboratory in San Diego, demonstrated that before entry into SWS, there is a cessation of movements[9] (see Fig. 2). Relevant to this point is that the patient with sleep apnea, with his frequent awakenings and movements, may never enter SWS. In their paper, Muzet *et al.*[9] noted that the presence or absence of body movements during stage 2 sleep can be useful as a predictor of the future course of sleep. While one

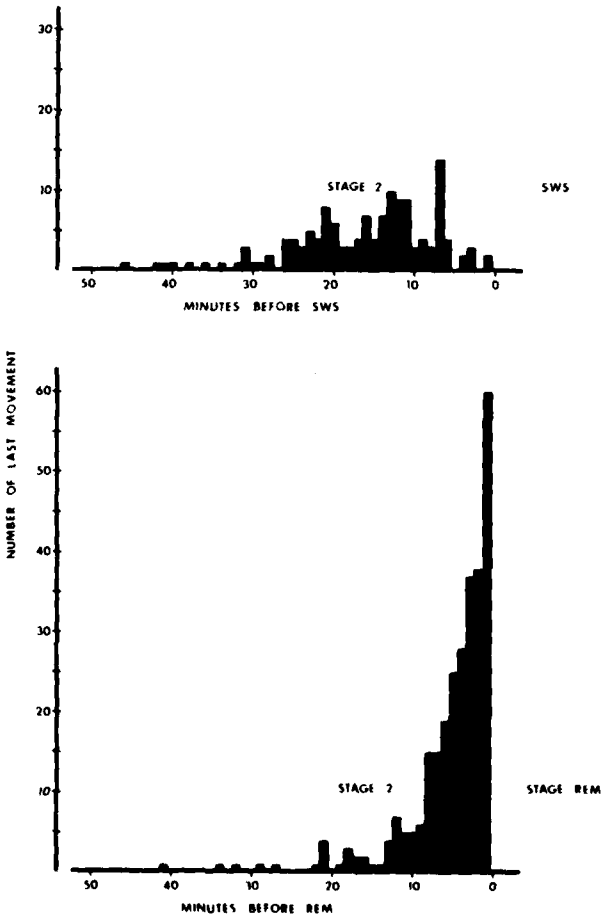


Fig. 2. Elapsed time since the last movement in stage 2 preceding SWS and REM sleep (from Muzet *et al.*[9]).

cannot predict that all periods without movement in stage 2 will be followed by SWS or that a movement in stage 2 will be followed by REM sleep, one can predict that there is a low probability (i.e., 14% of the time for the first SWS period and only 7% of the time after the first SWS) that stage 2 will change to SWS within the next 10 minutes after a body movement. This suggests that a body movement, and its associated increase in arousal level, is incompatible with the transition from stage 2 to SWS. In contrast, movements do not interfere with the transitions from stage 2 to REM sleep.

Time in Sleep Stages. Before turning to specific sleep and drug studies, I have been impressed that in the papers detailing the sleep of epileptics, especially those by Dr. Moulinier, a characteristic pattern is reported. In the nonmedicated or noncontrolled seizure patient, there is a high percent of awake time during the sleep period and a decrease in REM sleep. During effective treatment, awake time decreases and REM sleep increases. Before and during treatment, NREM sleep remains constant. Though there may be some changes in the composition of NREM sleep, i.e., amounts of stages 2, 3 and 4, the total NREM time remains remarkably consistent. I know of no unique function served by SWS and, thus, it is the amount of NREM sleep that appears to be most important and not the time spent in any particular sleep stage.[6] REM, not NREM sleep, however, is that part of sleep that appears most easily given up or disrupted.

A similar pattern is found when the effects of drugs on sleep stages are examined. Acute administration of barbiturates produces changes similar to that found with most drugs; that is, REM time and REM percent are reduced.[10] This alteration is illustrated in Fig. 3. Though there may be a decrease in SWS, resulting in an increase in stage 2, the total NREM sleep is less affected. The REM cycle is not significantly changed by barbiturates, reflecting the stability of

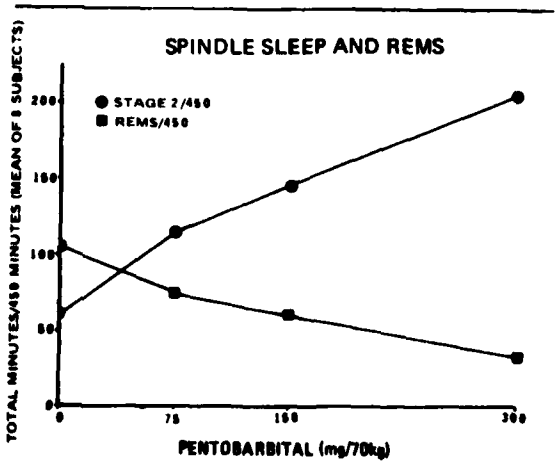


Fig. 3. Pentobarbital significantly ($P < 0.001$) decreased REMs and significantly ($P < 0.001$) increased spindle (stage 2) sleep. The mean of 8 subjects is expressed on the abscissa for each dose of pentobarbital in milligrams/70 kg. Each measure is expressed on the ordinate as total minutes during the 450 minutes after lights out, and is paired with its arithmetic regression equation (from Kay[10]).

this oscillation between REM and NREM sleep. REM sleep is decreased and stage 2 sleep is increased by non-barbiturate sedatives such as chloral hydrate, glutethimide and methaqualude, single doses of alcohol, and by benzodiazepines such as flurazepam, diazepam, triazolam and clonazepam. For the benzodiazepines, the increase in stage 2 is due more to the decrease in SWS than to a marked decrease in REM sleep.

Though normal subjects were studied, the most detailed report of DPH has been given by Zung.[8] In his study, DPH 100 mg, b.i.d., was administered to 10 normal adults, aged 20–46. All-night EEG and EOG (electro-oculogram) recordings were obtained for a total of 80 nights (4 control and 4 drug nights per subject). Comparison between control and drug nights indicated that DPH affected the sleep-REM activities as follows: The percent time spent in sleep stages 1 through 4 was unchanged, while percent REM time decreased significantly. There was no significant change between control and drug nights in the fluctuations from one sleep stage to another during the all-night sleep. The results from the drug studies, particularly the acute studies, support the view that REM sleep is the period of sleep most susceptible to external and internal influences.

Effect of Drugs on Sleep Spindles. References to these unique sleep rhythms have appeared in several of the presentations at this symposium. Dr. Barry Sterman and his associates, in past studies, have linked the sleep spindle with the sensorimotor rhythm, and have been particularly interested in the role of these wave forms in the control of seizures.[11,12] The linking of the sensorimotor rhythm and sleep spindles has also been questioned.[13]

I view sleep spindles as the unique and signature EEG rhythm of sleep. For me, sleep onset is defined as the appearance of the first sleep spindle, or at the first K-complex with its associated sleep spindle. Sleep spindles, in my opinion, have no relationship to seizure activity; they are a positive electrophysiological indicator of the stability of the sleep process. We will see, in a few minutes, that most CNS depressant drugs tend to enhance sleep, and ingestion of these drugs leads to an increase in sleep spindles.

Kay,[10] in his review, often comments that spindle sleep is increased following administration of most drugs, but he does not present data as to whether this is an increase in stage 2 or an actual increase in spindle rate/minute. Quantitative studies have indicated that, for most CNS depressants, both stage 2 time and spindle rate/minute are increased. This spindle increase is most striking for the benzodiazepines, as illustrated in Fig. 4,[14-16] but the increase in spindle rate/minute is also seen in patients after chronic use of pentobarbital[10] (see Fig. 5). Can the anti-convulsant properties of the drugs be implicated as the causal factor in the increase in sleep spindles? I think such an inference would be difficult to support. We have seen an increase in spindles in chronic alcoholics, and, as illustrated in Fig. 6, Azumi and Shirakawa (personal communication) find an increase in spindle rate with methaqualone, which is generally not thought of as an anti-convulsant. The other drug in Fig. 6 is flunitrazepam, a benzodiazepine, and the sleep spindle increase with this drug was expected. Increase in sleep spindles appears to be a consistent finding with drugs that depress the CNS. Most anti-convulsant medications have a CNS sedative component; thus, the increase in sleep spindles and decrease in seizures are probably due to this common CNS action, but I question whether the anti-convulsant action per se is causally related to the increase in sleep spindle rate.

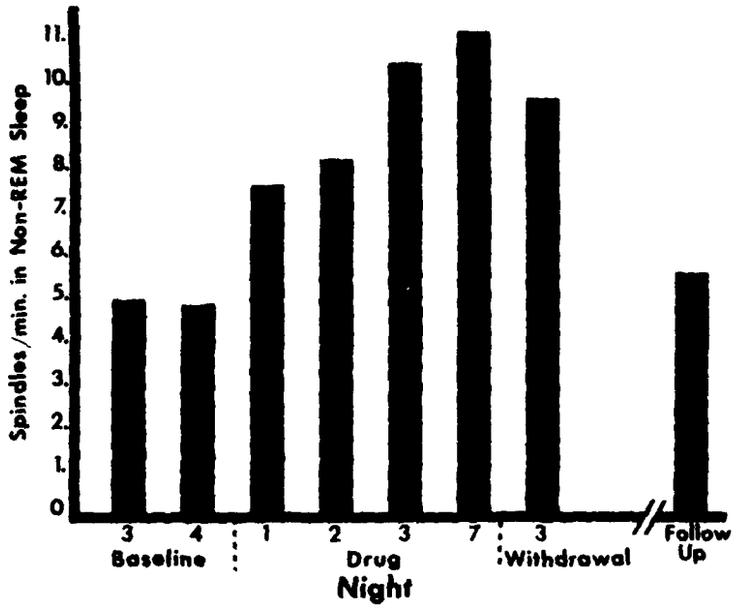


Fig. 4. Mean spindle rate/minute before (baseline), during (drug), and following (withdrawal) nightly ingestion of flurazepam 30 mg. Follow-up was 4–6 weeks post-drug.

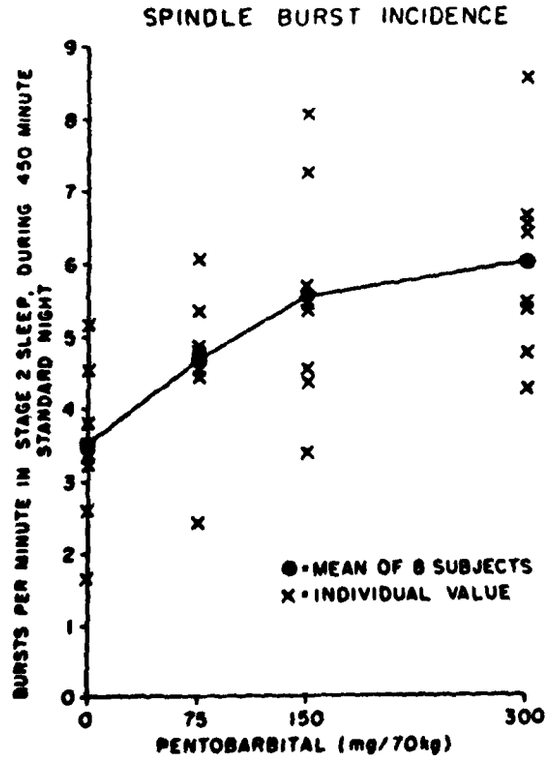
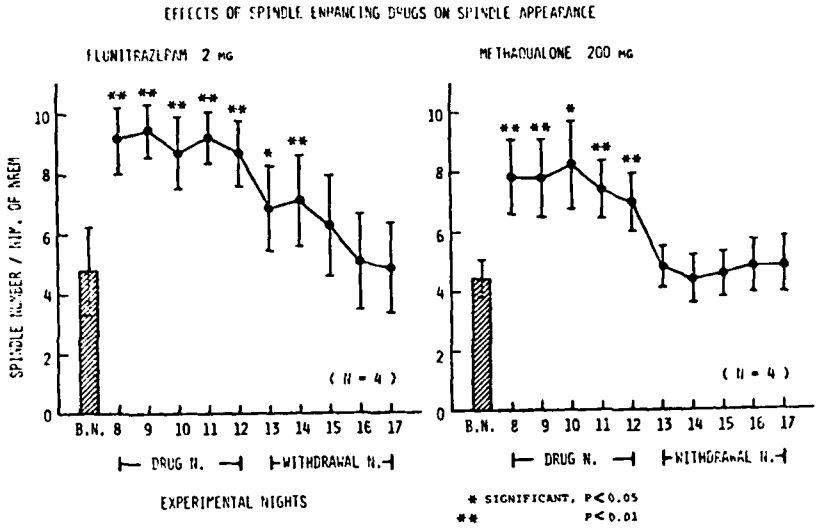


Fig. 5

Spindle burst incidence was significantly ($P < 0.05$) increased by pentobarbital. Each X represents the value for one subject, and each O represents the mean of 8 subjects. The dose of pentobarbital is expressed on the abscissa in milligrams/70 kg. Spindle burst incidence is expressed on the ordinate as bursts/minute of spindle sleep during the 450 minutes after lights out (from Kay[10]).



(With permission of Azumi & Shirakawa)

Fig. 6. Effects of spindle enhancing drugs on spindle appearance in the drug and withdrawal phases. Left graph: Flunitrazepam study; Right graph: Methaqualone study. Ordinate: Mean number of spindles/minute of NREM sleep time; Abscissa: Baseline and the 8th to 17th nights of experimental period. *, ** The averaged rates are significantly different from that of the baseline ($P < 0.05$ and $P < 0.01$, paired t-test, 2-tailed).

Chronic Effects. What are the effects of long-term use of anti-convulsants on sleep patterns? Again, the data are limited and seldom is a patient on a single medication or a stable medication regimen. The drugs, dose level, and pattern of administration frequently change for patients as they grow older and their seizure patterns change. Tolerance also undoubtedly develops. While the overall sleep pattern may not be remarkable and the patient reports no sleep complaints or hangover effects, we are accumulating data in our laboratory that suggest that the EEG changes seen with chronic benzodiazepine use do not show a tolerance effect.[15] These EEG changes appear to plateau, however, and this plateau appears to occur earlier with the short-acting benzodiazepines.[16]

A dramatic example of the failure of EEG tolerance to develop during prolonged use of a benzodiazepine was recently collected in our laboratory. A 34-year-old male had been taking flurazepam 30 mg for 4 years because of a sleep problem. He reported no daytime hangover effects and wondered whether the sleep medication was really still effective, but he was afraid to stop taking his "sleeping pill." During 371 minutes of EEG-recorded sleep, he showed only stage 2 and REM. There were so few slow waves of 75 μV amplitude that no page could be scored as stage 3 or 4 sleep. K-complexes were very infrequent, but there were numerous sleep spindles. Stage 2 percent was 65 and REM was 35%. The REM-NREM cycle length was 88 minutes. An example of the two types of sleep are presented in Fig. 7. I have been impressed that when there is no SWS, there are few K-complexes in stage 2. It appears that vertex sharp waves are forerunners of the K-complex, and the K-complex heralds the appearance of high amplitude slow waves.

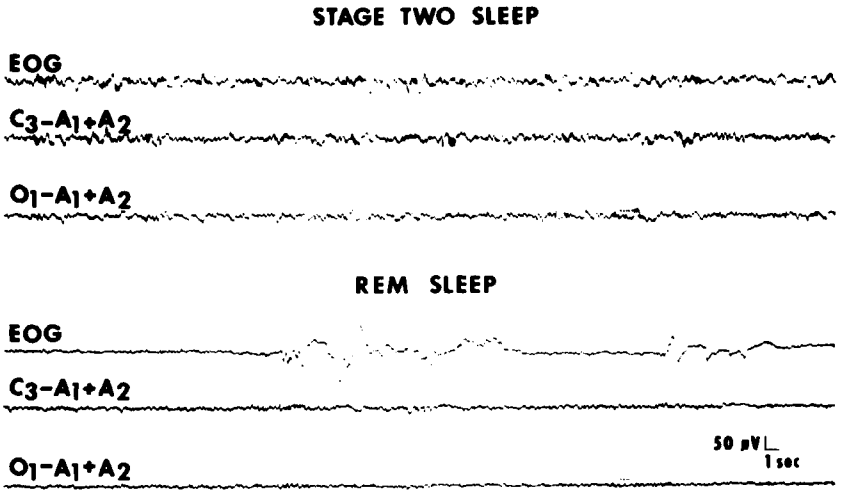


Fig. 7. Example of the two types of sleep in a patient after nightly use of flurazepam 30 mg for over 4 years. Stage 2 was sample of record 50 minutes after sleep onset. Note absence of high amplitude delta waves and K-complexes.

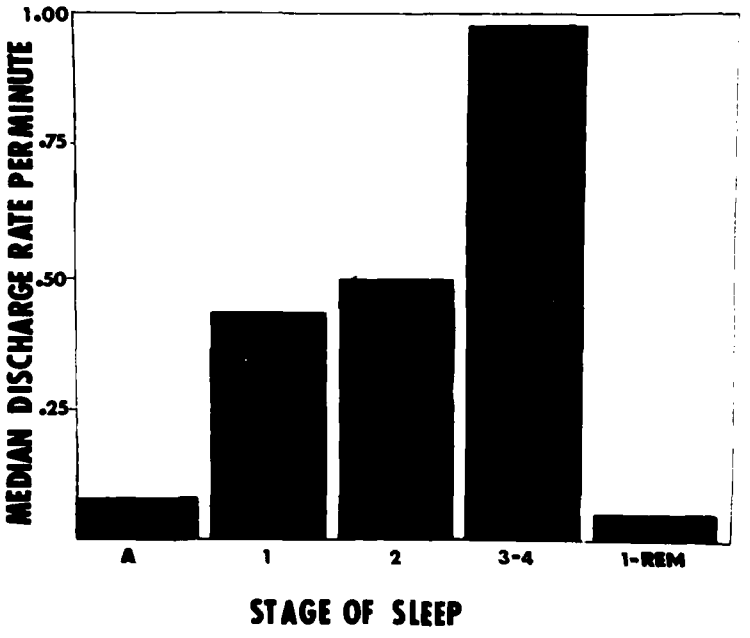


Fig. 8. Median rate of EEG seizure activity during presleep awake and stages of sleep (from Ross *et al.*[17]).

Returning to the sleep patterns in seizure patients, we found normal sleep patterns in a group of patients in San Diego who had been on anti-convulsant medication from a few months to several years.[17] In Fig. 8 is the pattern of nocturnal seizure discharge rate in these 12 patients. Note the similarity of the discharge rate between awake and REM. These patients all had generalized seizures and seizure activity when awake. Though the seizure discharge rate increased with sleep, there was no myoclonic activity and the patients did not awaken during or after the seizure activity. In Table 1 are the sleep stage percents. Note the similarity in the sleep stages in the epileptic and nonepileptic groups.

TABLE 1

TOTAL MEAN PERCENTAGE OF SLEEP BY STAGE IN MEDICALLY CONTROLLED SEIZURE PATIENTS (from Ross *et al.*[17])

Stage	Epileptics	Nonepileptics
Wake	8.7	9.3
REM	19.8	17.0
1	3.6	4.7
2	46.1	48.4
3	13.4	10.5
4	8.1	10.0

In summary, there are few good sleep studies detailing the effects of most anti-convulsants on sleep patterns. The studies that have been done indicate that anti-convulsant effect on sleep is similar to that of other drugs that depress the CNS. It is unlikely that these EEG sleep changes are causally related to the anti-convulsant properties of this class of drugs. The most common report is that anti-convulsants "stabilize" or "normalize" the sleep pattern. This stabilization is most often seen when the anti-convulsant reduces the nocturnal seizures, especially myoclonic seizures. The reduction of the myoclonic activity allows the normal progression of sleep to occur and, in particular, allows the patient to enter SWS.*

* Since my presentation, Wolf and Röder,[18] in an abstract, noted that ethosuximide (ES) and sodium valproate (VPA) produced different effects on sleep organization in 6 epileptic patients. With ES, deep sleep stages decreased, REM sleep percentage increased, the percentage of time awake during the night increased as well as stage 1 (drowsiness). VPA, in contrast, seemed to have only minor effects on sleep.

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4. TITLE *(and Subtitle)*: (U) Effects of Anti-Convulsant Medication on Sleep Patterns	5. TYPE OF REPORT & PERIOD COVERED: Interim
	6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s): Laverne C. JOHNSON	8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Naval Health Research Center, P.O. Box 85122, San Diego, CA 92138	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: MR041.01.003-0157
11. CONTROLLING OFFICE NAME AND ADDRESS: Naval Medical Research and Development Command, Bethesda, MD 20014	12. REPORT DATE: August 1981
	13. NUMBER OF PAGES: 13
14. MONITORING AGENCY NAME & ADDRESS *(if different from Controlling Office)*: Bureau of Medicine and Surgery, Department of the Navy, Washington, DC 20372	15. SECURITY CLASS. *(of this report)*: Unclassified
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

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Anti-convulsants
Sleep
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20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

(U) A review of the literature revealed few studies detailing the effects of anti-convulsants on sleep structure and pattern. Most studies have used barbiturates, and the effects of this class of drug appear to be the same whether the barbiturate is prescribed as an anti-convulsant or sedative-hypnotic. The same sleep changes are also found for the benzodiazepines used as a sedative-hypnotic and as an anti-convulsant. Acute studies indicate that anti-convulsants decrease

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S/N 0102-014-6601

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SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

20. ABSTRACT (continued)

REM sleep, while chronic ingestion decreases SWS, but total amount of NREM sleep is less affected. Sleep spindles usually are increased. An epileptic patient's sleep pattern is most likely to be more normal or stabilized after effective treatment. This normalization appears to be due to the control of nocturnal seizures, which previously disrupted sleep, rather than due to any effect of the anti-convulsant per se on sleep patterns.


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